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Efficacy and Safety of Neoadjuvant Immunotherapy Combined with Sandwich Chemoradiotherapy in Locally Advanced Nasopharyngeal Carcinoma: A Retrospective Study

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Purpose: We aimed to determine the safety and feasibility of neoadjuvant immunotherapy combined with sandwich chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma (NPC).

Patients and Methods: This retrospective study involved 37 patients with locally advanced NPC treated with the above regimen. All patients received four cycles of neoadjuvant immunotherapy and chemotherapy at three-week intervals, including the administration of PD-1 inhibitors, namely, sintilimab (a fixed dose of 200 mg on Day 1) or toripalimab (240 mg on Day 1). The chemotherapy program consisted of nab-paclitaxel (260 mg/m2, Day 1) plus nedaplatin (85 mg/m2, Day 1). Concurrent with intensity-modulated radiation therapy (IMRT), the patients received targeted drug therapy with nimotuzumab (200 mg) across six cycles. Finally, 4 cycles of S-1 adjuvant chemotherapy were administered.

Results: In this study, the efficiency of neoadjuvant immunotherapy combined with chemotherapy was 94.6%, the CR rate was 67.6%, and the efficiency 3 months after IMRT was 100%. The 2-year overall survival (OS), locoregional control (LCR), distant metastasis-free survival (DMFS), and progression-free survival (PFS) rates of the whole group were 97.3%, 94.6%, 97.3% and 91.9%, respectively. Neutropenia was the most common hematological toxicity (100%), and the incidence of grade ≥ 3 neutropenia was 40.5%. Grade 3 anemia and thrombocytopenia did not occur. Additionally, no adverse reactions, such as hypothyroidism, immune pneumonia, or myocarditis, occurred in the whole group. However, the incidences of rash, musculoskeletal pain, and hepatotoxicity were high (45.9%, 54.1% and 37.8%, respectively).

Conclusion: The survival benefit of neoadjuvant immunotherapy combined with sandwich chemoradiotherapy is excellent, with tolerable toxicity, in patients with locally advanced NPC. This study provides new insight into the application of immunotherapy in locally advanced NPC.

Keywords: chemotherapy, immunotherapy, intensity-modulated radiation therapy, nasopharyngeal carcinoma, prognosis

Nasopharyngeal carcinoma (NPC) is a malignant tumor that occurs in the nasopharyngeal mucosa and is one of the most common malignant tumors of the head and neck in China and Southeast Asia. The most common pathological type is undifferentiated non-keratinizing carcinoma, the pathogenesis of which is associated mainly with persistent EBV infection, genetic susceptibility, smoking, alcohol consumption, pickled food, and oral hygiene.[1,2] According to

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the seventh edition of the AJCC staging system, the 5-year OS rates of patients with stages I, II, III, IVa, and IVb disease are 100%, 94.6%, 88.1%, 80.5% and 72.1%, respectively.[3] From 1990 to 2010, the distant metastasis-free survival (DMFS) rate of stage IVb N3 patients was approximately 79% and did not significantly improve.[3] The standard treatment for locally advanced NPC is concurrent radiotherapy and chemotherapy, but after receiving concurrent radiotherapy and chemotherapy, approximately 30% of patients still experience recurrence and metastasis. In recent years, scholars at home and abroad have hoped to further reduce the risk of recurrence and metastasis, thereby improving the survival rate of patients by using a combination of adjuvant chemotherapy or induction chemotherapy on the basis of concurrent chemoradiotherapy, and some results have been obtained; however, these results are still not satisfactory.[4–6]

Since NPC is closely associated with EBV infection, the expression of EBV-related proteins can stimulate a virus-specific immune response. Virus-associated tumors often manifest as "inflammatory tumors", with high expression of PD-L1 and abundant lymphocyte infiltration. PD-L1 positivity reached 89–95% in NPC patients, and most patients expressed TPSs at a rate of more than 50%, suggesting that this cancer is more likely to benefit from immunotherapy.[7] The CONTINUUM study is the world's first Phase III clinical study of immunotherapy combined with chemo-radiotherapy for the treatment of locally advanced NPC. Compared with that of the control group, the 3-year event-free survival (EFS) rate of the sintilimab treatment group was significantly increased by 10% (86.1% vs 76%, HR 0.59, p=0.019), and the risk of recurrence, metastasis and death was reduced by 41%. However, in the immunotherapy group, 2 patients died due to immune drug-related toxicity,[8] which suggests that how to safer and more effectively use immunotherapy in locally advanced NPC patients is questionable and a direction for further research.

A characteristic feature of NPC is the overexpression of epidermal growth factor receptor (EGFR), and high EGFR expression is associated with targeted drug therapy in 68–89% of patients. Nimotuzumab, a monoclonal antibody drug targeting the epidermal growth factor receptor, is the first humanized monoclonal antibody drug that can competitively inhibit the binding of endogenous ligands to EGFR, block the downstream signaling pathway mediated by EGFR, and prevent antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), which lead to the endocytosis and degradation of EGFR and the killing of tumor cells.[9] Nab-paclitaxel is a novel paclitaxel preparation that uses albumin as a solvent. Compared with traditional paclitaxel preparations, it has stronger antitumor ability and fewer toxic side effects, such as hematotoxicity and severe allergic reactions. It is convenient to use and does not require special infusion equipment or anti-allergic pretreatment.[9] Nab-paclitaxel has been shown to have a better treatment effect than conventional solvent-based paclitaxel in NPC patients. Nedaplatin is a second-generation platinum antitumor drug. The antitumor effect of nedaplatin is better than that of cisplatin, with different toxicity profiles. The incidence of major adverse reactions, such as gastrointestinal reactions, was significantly lower than that of cisplatin. Combined radiotherapy for advanced cancer can improve the efficacy and survival rate and significantly reduce adverse reactions.[10]

Previous studies at our center confirmed that nab-paclitaxel plus cisplatin and nimotuzumab combined with IMRT, followed by S-1 adjuvant chemotherapy, yielded excellent survival benefits with tolerable toxicity in patients with stage N3 NPC. The 3-year locoregional control, overall survival, distant metastasis-free survival, and progression-free survival rates were 97.6%, 87.6%, 83.5%, and 81.0%, respectively.[9] The treatment model based on the early stage achieved a very good treatment effect. Moreover, whether the addition of immunotherapy treatment can improve survival is unknown. This study aimed to determine whether patients with locally advanced NPC could be optimally treated via a regimen of neoadjuvant immunotherapy combined with sandwich chemoradiotherapy.

Patients and Methods

Ethics and Consent

The study protocol was approved by the ethics committee of Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University (NO:2024–727), Haikou, China. Our study complies with the Declaration of Helsinki. Each patient provided informed consent.

Patient Selection

This retrospective study involved 37 patients who received treatment for locally advanced NPC at Hainan General Hospital between May 2020 and January 2022. All patients had pathologically confirmed nonkeratinizing NPC with no distant metastases. The baseline examination included the following examinations: plasma EBV DNA load, magnetic resonance imaging (MRI) of the head and neck, and positron emission tomography to exclude distant metastasis. PET–CT was used when the tumor was difficult to differentiate. Cancer staging was performed via the TNM classification system of the American Joint Committee on Cancer (eighth edition).

Intensity-Modulated Radiation Therapy

The gross tumor volumes of primary nasopharyngeal tumors (GTVnx) and positive neck lymph nodes (GTVnd) were calculated via MRI. Based on MRI, the GTVnx before the neoadjuvant therapy, defined as GTVpre, was given a radiation dose of 66 Gy; the residual lesion after neoadjuvant therapy, defined as GTVpost, was given a radiation dose of 70 Gy, and the region with bone invasion was given a radiation dose of 70 Gy. In addition, the high-risk area and the low-risk area were given a radiation dose of 60 Gy and 56 Gy, respectively, for a total of 32 fractions. At the same time, the posterior margin of GTVnx was covered by the isodose curve of 66 Gy whenever possible. For this reason, we specifically relaxed the restriction of the brainstem. Any volume <10% of 3 mm brainstem with a planning organ at risk volume (PRV) of more than 60 Gy and is considered acceptable We observed the long-term follow-up results of hundreds of patients, and brainstem injury and necrosis were not found.

Drug Administration

All patients received four cycles of neoadjuvant immunotherapy and chemotherapy at three-week intervals, including the administration of PD-1 inhibitors: sintilimab (a fixed dose of 200 mg on Day 1) or toripalimab (240 mg on Day 1). The chemotherapy program consisted of nab-paclitaxel (260 mg/m2, Day 1) plus nedaplatin (85 mg/m2, Day 1). Concurrent with intensity-modulated radiation therapy (IMRT), the patients received targeted drug therapy with nimotuzumab; a 200-mg dose was infused with IMRT across six cycles. Finally, adjuvant chemotherapy was started within 4 weeks after the end of radiotherapy, and S-1 adjuvant chemotherapy was administered. The S-1 dose was determined according to the body surface area (BSA) as follows: BSA < 1.25 m2, 40 mg twice a day; 1.25 m2 ≤ BSA < 1.5 m2, 50 mg twice a day; and BSA ≥ 1.5 m2, 60 mg twice a day. A single cycle of adjuvant chemotherapy took 42 days. S-1 was administered for the first 28 days and then stopped for 14 days. We planned to administer 4 cycles of S-1 adjuvant chemotherapy to each patient.

Efficacy and Safety Assessments

The primary endpoint was the OS rate. The secondary endpoints were the objective response rate (ORR) and toxicity rates. The treatment efficacy was assessed via the Response Evaluation Criteria in Solid Tumors and categorized as follows: complete response (CR), partial response (PR), stable disease, and progressive disease. The ORR was calculated as the sum of the CR and PR rates. Adverse events (toxicities) were classified via the Common Toxicity Criteria v3.0 issued by the National Cancer Institute.

Statistical Analysis

Data were processed via the SPSS 25.0 software package (IBM Corp). The LRC, OS, DMFS, and progression-free survival (PFS) rates were calculated via the Kaplan–Meier method, and differences in these rates were analyzed using the Log rank test. Relevant factors were screened via the chi-square test. $P < 0.05$ was considered statistically significant.

Results

General Information

The follow-up rate of the whole group was 100%, and 37 patients completed 4 cycles of neoadjuvant immunotherapy combined with chemotherapy, as well as concurrent IMRT and nimotuzumab targeted therapy. Thirty-three patients

successfully completed 4 cycles of oral adjuvant chemotherapy; only 4 patients experiencing nausea and loss of appetite did not complete 4 cycles. The other clinical characteristics of the patients are shown in Table 1.

Response Rates

Considering that it is very rare for patients with metastatic lymph nodes to achieve a true complete remission (CR) after neoadjuvant chemotherapy, we chose primary nasopharyngeal lesions for short-term efficacy evaluation. For the evaluation of the efficacy of neoadjuvant therapy, we chose to perform the evaluation after completing four cycles of neoadjuvant immunization and chemotherapy and before the start of IMRT. The efficacy evaluation after chemotherapy and radiotherapy was performed three months after the end of IMRT. After neoadjuvant therapy, CRs were observed in 25 patients, whereas partial remissions (PRs) were observed in 10 patients. Thus, the short-term efficacy of neoadjuvant chemotherapy was 94.6%, with a CR rate of 67.6% [Table 2]. At 3 months after IMRT, the overall efficacy was 100.0%.

Table 1 Clinical Characteristics of Patients with Locally Advanced Nasopharyngeal Carcinoma

Parameter	Number of Patients	Percentage
Sex		
Men	27	73.0%
Women	10	27.0%
Degree of differentiation		
Undifferentiated	31	83.8%
Differentiated	6	16.2%
T classification		
T1	0	0%
T2	4	10.8%
T3	17	46.0%
T4	16	43.2%
N classification		
N1	6	16.2%
N2	18	48.7%
N3	13	35.1%
Clinical classification		
III	10	27.0%
IVA	27	73.0%
EBV DNA		
≥4.0E + 3 copies/mL	14	37.8%
<4.0E + 3 copies/mL	23	62.2%
PD-1 inhibitor		
Sintilimab	28	75.7%
Toripalimab	9	24.3%

Abbreviation: EBV, Epstein-Barr virus.

Table 2 Clinical Efficacy of the Treatment Regimens

Short-term CR, n (%) PR, n (%)	SD, n (%) PD, n (%)
Induction chemotherapy 25 (67.6) 10 (27.0)	1 (2.7) 1 (2.7)
Chemoradiotherapy 36 (97.3) 1 (2.7)	0 (0) 0 (0)

Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Safety

No adverse reactions, such as hypothyroidism, immune pneumonia, or myocarditis, occurred in the whole group. However, the incidences of skin rash and musculoskeletal pain were relatively high, at 45.9% and 54.1%, respectively. Notably, a total of 14 patients had abnormal liver function, mainly due to increased alanine transaminase and aspartate transaminase levels. Neutropenia is the most common hematological toxicity, occurring in 100% of patients. The incidence of grade 3 or higher neutropenia was 40.5%. Grade 3 or higher anemia and thrombocytopenia were not observed [Table 3]. Since no synchronized chemotherapy was used, the overall radiation-induced oral mucositis was mild and well tolerated. The patient's weight loss was not significant, which also laid the foundation for the smooth completion of oral chemotherapy for the patient after IMRT.

Treatment Failure

The median follow-up period was 37 months (range, 14–50 months). There was only one death in the whole group. Figure 1 shows the patient experiencing nasopharyngeal progression after neoadjuvant therapy. After the end of IMRT, the patient began taking S1 chemotherapy orally. Owing to the detection of multiple bone and liver metastases during follow-up, treatment was changed to the GP regimen; however, the disease still progressed rapidly, and the patient died. In addition, two patients experienced recurrence. One patient experienced recurrence of the left level 2 lymph node half a year after IMRT. After surgical resection, no other abnormalities were found during follow-up. Another patient experienced recurrence at the left petrous apex more than 2 years after IMRT. The patient was treated with immunization combined with the GP regimen, after which immunotherapy was used as maintenance treatment. No other abnormalities were found during the follow-up.

Survival Rates

The 2-year OS, locoregional control survival (LCS), DMFS, and progression-free survival (PFS) calculated via the Kaplan–Meier method were 97.3%, 94.6%, 97.3% and 91.9%, respectively. The 95% confidence interval of OS was 41.682–44.869, that of LCS was 39.824–44.740, that of DMFS was 41.500–44.927, and that of PFS was 38.557–44.333 [Figures 2–5]. Because the overall failure rate was very low, no clinical features or indicators closely related to predicting treatment efficacy were found via statistical analysis.

Discussion

NPC is one of the most common malignant tumors of the head and neck in China and is concentrated mainly in southern coastal areas. NPC represent the phenomenon of the population susceptibility, with obvious regional aggregation, racial susceptibility, a tendency toward a high incidence in families, and relatively stable incidence rates. Since the 1970s, multiple EBV antibody based screenings have been shown to improve the early diagnosis rate and the survival rate of NPC. Recently, a randomized controlled screening study confirmed for the first time that the use of EBV antibody screening can significantly reduce the mortality rate of NPC in the screening area by 30%, with the most significant

Table 3 Treatment-Related Toxicities in the Acute Stage

Adverse Reaction	Grade I + II	Grade III + IV	n (%) Total (N=103)
Neutropenia	22	15	37(100%)
Anemia	29	0	29(78.4%)
Thrombocytopenia	2	0	2(5.4%)
Hepatotoxicity	14	0	14(37.8%)
Rash	17	0	17(45.9%)
Musculoskeletal pain	20	0	20(54.1%)
Fatigue	17	0	17(45.9%)
Nausea	9	0	9(24.3%)
Mucositis	33	3	36(97.3%)
Limb numbness	11	0	11(29.7%)

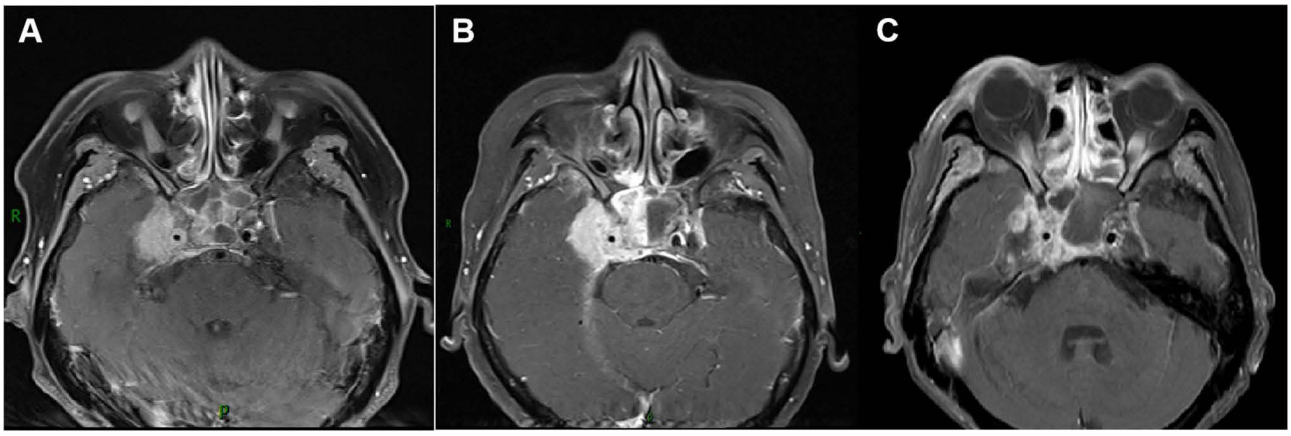

Figure 1 MRI scan of the patient experiencing nasopharyngeal progression after neoadjuvant therapy. (**A**) The baseline of the tumor. (**B**) Tumor progression after neoadjuvant therapy. (**C**) Partial remission of the tumor after IMRT.

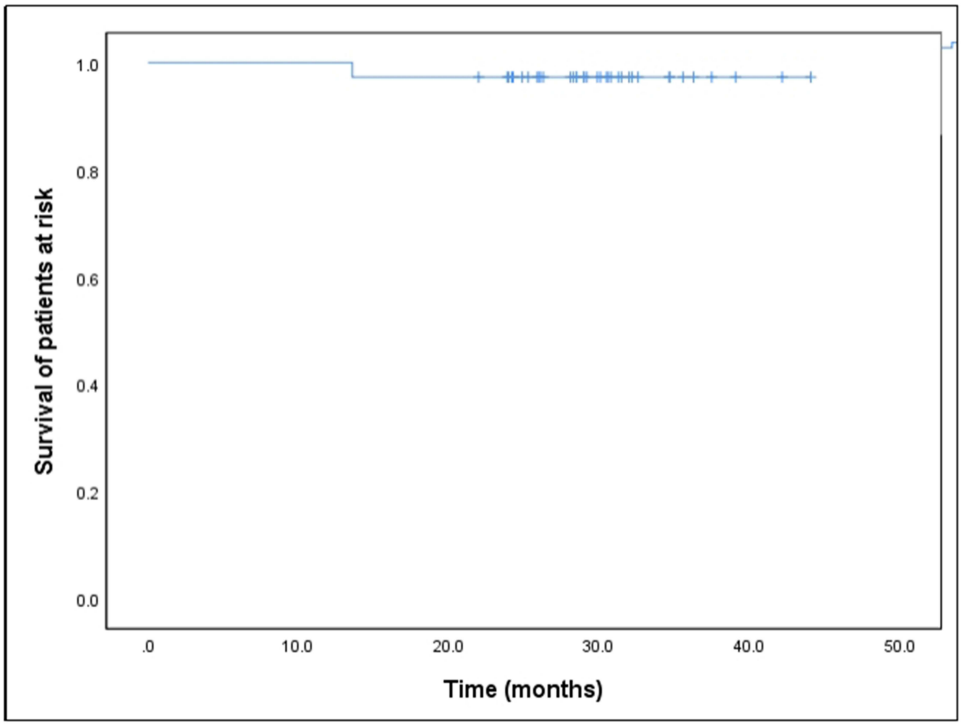

Figure 2 Overall survival rate of patients with locally advanced NPC treated with neoadjuvant immunotherapy combined with sandwich chemoradiotherapy, as estimated using the Kaplan-Meier method.

benefit in the population aged 50 and above.[11] For a long time, chemoradiotherapy has been the main treatment approach for locally advanced NPC; however, efficient and low-toxicity targeted drugs and new treatment methods are lacking, and treatment efficacy of NPC has gradually reached a bottleneck. With the widespread application of IMRT in NPC, the local control rate has been greatly improved. Although the radiation related toxicity has been significantly reduced, there are still some radiation therapy related toxicities that are receiving increasing attention, such as radiation-induced osteonecrosis with a high incidence rate, which is difficult to treat and sometimes difficult to distinguish from local tumor recurrence. Osteonecrosis is most likely to occur in the mandible and is related to smoking, local inflammation, etc. It requires us not only to control the dosage, but also to manage the hygiene of the local environment to reduce the impact of inflammation on bone erosion.[12,13] The efficacy of neoadjuvant chemotherapy for locally advanced NPC are

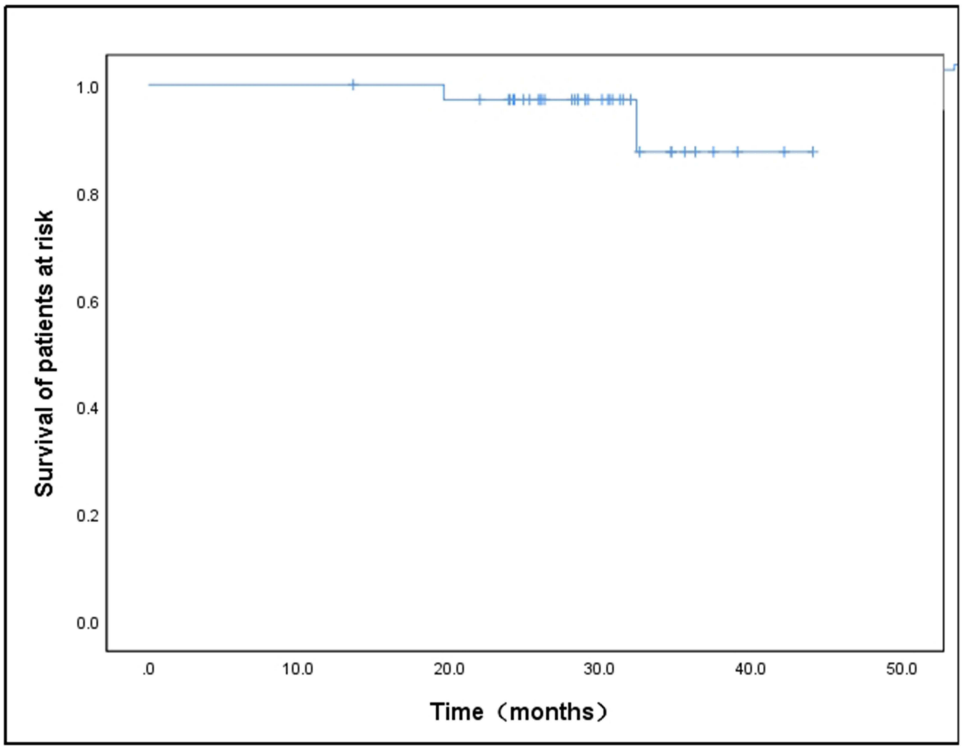

Figure 3 Locoregional control rate of patients with locally advanced NPC treated with neoadjuvant immunotherapy combined with sandwich chemoradiotherapy, as estimated using the Kaplan-Meier method.

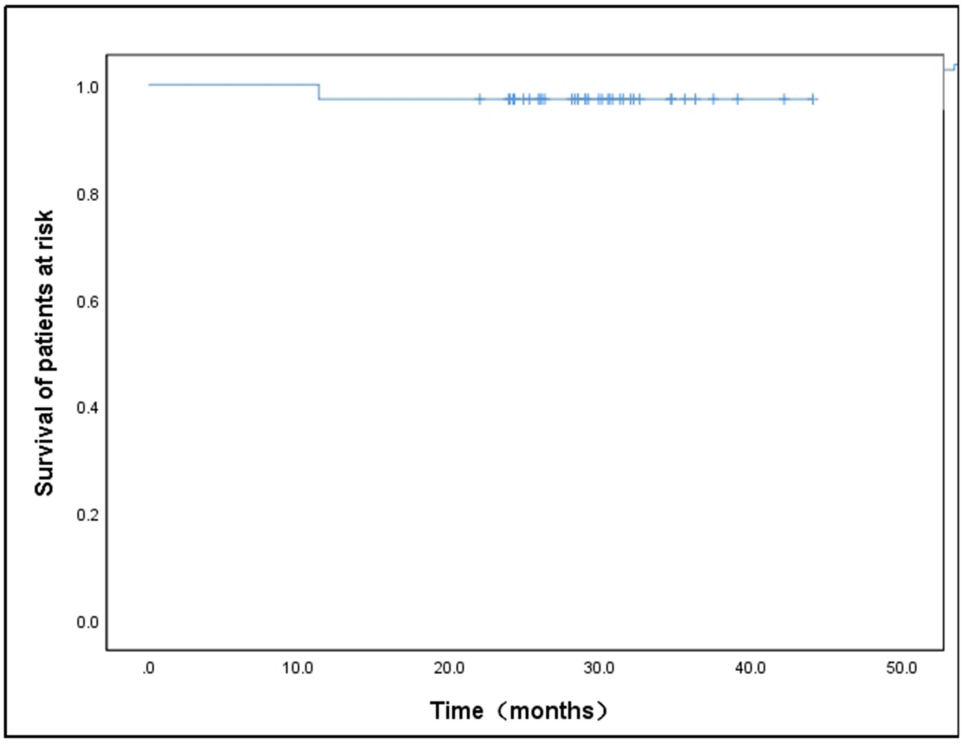

Figure 4 Distant metastasis-free survival rate of patients with locally advanced NPC treated with neoadjuvant immunotherapy combined with sandwich chemoradiotherapy, as estimated using the Kaplan-Meier method.

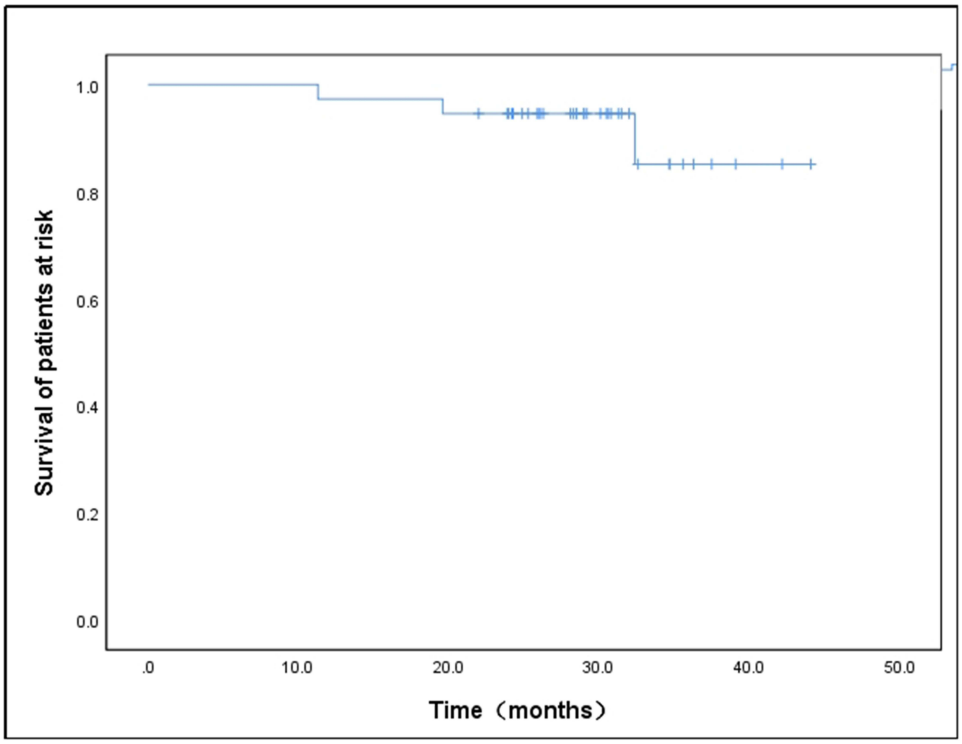

Figure 5 Progression-free survival rate of patients with locally advanced NPC treated with neoadjuvant immunotherapy combined with sandwich chemoradiotherapy, as estimated using the Kaplan-Meier method.

closely related with the final treatment efficacy. After neoadjuvant chemotherapy, the PFS of patients who achieved CR and PR was better than that of patients with SD or PD, and the PFS and OS of patients with zero copy numbers of EB virus were better than those of patients without zero copy numbers.[14,15] It is important to choose reasonable and effective treatment methods to improve the survival rate, reduce adverse reactions, and improve the quality of life of patients with NPC. Many clinical studies have shown that neoadjuvant chemotherapy can significantly improve the LCS or the absence of distant metastasis in NPC.[14–16] This experiment was based on a previous clinical study at our center.[9] We aimed to improve the overall prognosis of patients with locally advanced NPC by further improving the efficacy rate of neoadjuvant therapy.

In recent years, the use of nedaplatin and nab-paclitaxel for the treatment of NPC has gradually attracted the attention of medical experts. They can not only effectively improve clinical efficacy but also reduce nausea, vomiting, nephrotoxicity and other related adverse reactions caused by chemotherapeutic drugs. Currently, tumor immunotherapy has received widespread attention in clinical practice. The hotspots in the field of tumor immunotherapy are focused mainly on immune checkpoint inhibitors such as programmed death-1 (PD-1) receptors, which is a new type of antitumor therapy. The concept is to kill tumors by reactivating the patient's own immune cells. In addition, chemotherapy and radiotherapy can release tumor antigens, increase tumor antigen presentation, and enhance the antitumor effect, so radiotherapy and/or chemotherapy combined with immunotherapy can have a synergistic effect. Toripalimab and sintilimab are the first PD-1 mAbs approved for production in China. Their mechanism of action involves blocking the binding of PD-1 on T lymphocytes to programmed death ligands on the surfaces of tumor cells (PD-L1), thus releasing the immunosuppression of immune cells from tumor cells and allowing immune cells to play the role of anti-tumor cell immunity again to kill tumor cells.[8,17,18]

In this study, the efficacy of neoadjuvant immunotherapy combined with chemotherapy was 94.6%, the CR rate was 67.6%, and the efficacy 3 months after radiotherapy was 100%. Because the copy number of the EB virus in our hospital cannot detect whether it is zero, we only use a cutoff value of 500 to determine whether it is positive or negative. Before the second cycle of chemotherapy, 70.3% of patients turned negative, and before the third cycle of chemotherapy, 97.3%

of patients turned negative. Only one patient in the entire group who progressed first decreased, and then increased again from the beginning of the third cycle. The evaluation of short-term efficacy was jointly performed by the doctors in the radiotherapy department, the radiologist, and the otolaryngologist on the basis of MRI and endoscopy. The main results were that no mass shadow or enhancement shadow was found on the MR images and that the nasopharyngeal mucosa was smooth under nasal endoscopy. A mucosal protrusion or tumor was found. In addition, we found that even patients who were insensitive to neoadjuvant therapy were very sensitive to IMRT, and all patients achieved CR after radiotherapy, suggesting that even if NPC is insensitive to chemotherapy, it does not mean that it is insensitive to radiotherapy. The only death was a result of progression that due to non-response to neoadjuvant therapy. The copy number of the EB virus reached the maximum level of 500,000 copies/mL. The therapeutic regimen was changed to a second-line chemotherapy regimen, which included PD-1 combined with GPs and PD-1 combined with angiogenic drugs. The tumor was stable for a very short time; however, it progressed again after no more than 2 months. Owing to the subsequent decrease in platelet count, the tumor did not invade the bone marrow. The patient died of multiorgan failure due to the inability to continue chemotherapy. Clinical studies have shown that NPC patients treated with IMRT with at least 66.5Gy during IMRT have significantly less locoregional failure.[19] Two patients experienced recurrence. One patient achieved CR in the nasopharyngeal region after neoadjuvant therapy. Two years after radical radiotherapy, the recurrence occurred at the left petrous apex. A review of the treatment plan revealed that a radiotherapy dose of 66 Gy covered the recurrence area. Current studies of radiotherapy for NPC tend to use a highly efficient attenuated treatment mode. To avoid radiation-induced temporal lobe injury or nerve injury, the reduced prescribed dose is often used for patients in whom neoadjuvant therapy is effective. However, the disease recurrence in this patient also suggests that even if a CR is achieved after neoadjuvant therapy, the radiotherapy dose should not be less than 66 Gy. Another patient was an elderly woman with recurrence in lymph node 2 on the left side of the neck. After radiotherapy, the patient completed only 2 cycles of adjuvant oral chemotherapy due to loss of appetite. Surgical resection was conducted after the recurrence, and no abnormality was seen in the subsequent regular follow-up evaluations.

The 2-year OS, LCS, DMFS, and PFS of the whole group were 97.3%, 94.6%, 97.3% and 91.9%, respectively. The 2-year results of this study are better than those of our center without combined immunotherapy in the early stage, similar to the results of current immunotherapy used for one year, but the toxicity of immunotherapy drugs is lighter.[8,9] During follow-up examinations, all patients were required to simultaneously attend consultations in the radiotherapy and otolaryngology departments. Intervention by an otolaryngologist can significantly reduce the incidence of sinusitis, otitis media, and nasopharyngeal mucosal erosion and necrosis in these patients. None of our patients developed pharyngeal hemorrhage or radiation-induced temporal lobe injury. Skin adverse reactions are among the most common adverse reactions associated with PD-1 mAbs, and the exact mechanism remains unclear. On the basis of our previous studies and considering the neurotoxicity and incidence of rashes associated with nab-paclitaxel, an interval of at least 2 hours between infusions of nab-paclitaxel and nedaplatin is needed. To avoid rash caused by combination chemotherapy with immunotherapy, we prophylactically used cetirizine tablets, fexofenadine hydrochloride tablets, vitamin C tablets and compound glycyrrhizin tablets after the end of chemotherapy. Even so, 17 patients still developed rashes of different degrees; the overall extent was small and could be alleviated with topical halometasone cream and intravenous infusion of methylprednisolone. Notably, a total of 14 patients had abnormal liver function, mainly due to increases in alanine transaminase and aspartate transaminase; most of these cases resolved on their own.

For pain that occurs after chemotherapy, we will educate patients in advance, and most of them will relieve themselves. If the pain is obvious, non steroidal analgesics should be taken orally. Only a small portion of the patients received treatment with hepatoprotective drugs, which was ineffective, and their liver functions were normal after steroid administration. Immune hepatitis was considered. Neutropenia is the most common hematological toxicity, occurring in 100% of patients. The incidence of grade 3 or higher neutropenia was 40.5%. Grade 3 or higher anemia and thrombocytopenia were not observed. At the same time, we found that patients with NPC often had strong reactions to synchronous chemotherapy and had difficulty completing the second and third cycles of concurrent chemotherapy. Targeted therapy with nimotuzumab was given to replace concurrent chemotherapy; patient compliance was excellent, oral mucositis was milder, the planned radiotherapy plan was successfully completed, and the overall recurrence and metastasis rates were very low.

Conclusion

In summary, neoadjuvant immunotherapy combined with sandwich chemoradiotherapy in locally advanced NPC has achieved very good therapeutic effects, with very low recurrence and metastasis rates, and the adverse reactions are tolerable. Although this is only a preliminary result of 2 years, this study has great clinical significance, considering that there is a peak period of recurrence and metastasis within 2 years after treatment for NPC. Large sample sizes and long-term results are still needed for further confirmation. In addition, immunotherapy was used only four times, the incidence of immune-related toxicity was very low, it was safer, and the economic burden was lower. Both time and economic costs have been greatly reduced, supporting the application of immunotherapy as a new treatment option for locally advanced NPC.

Ethics

This study was approved by the ethics committee of Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University (NO:2024-727). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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